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学 位 論 文

Change of Tinnitus with Xenon Phototherapy of the Stellate Ganglion

キセノン光を用いた星状神経節近傍照射療法による耳鳴苦痛度の変化

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Introduction

Tinnitus is defined as perceived sound originating in the head, and is a common complaint in clinical practice¹. However, the pathophysiology of tinnitus remains unclear, and thus it is difficult to develop definitive treatment strategies for underlying pathologies. No treatment modality has been established based on the guidelines. On the other hand, stellate ganglion block (SGB) was reported to be a possible treatment for tinnitus².

SGB has commonly been performed to improve pain and blood flow in patients with various diseases. However, SGB has not been widely accepted because of the risk of severe complications, lack of scientific evidence, and technical difficulty. Thus, owing to its minimal tissue invasiveness, bio-permeability, and optimal-range stable light energy, xenon light irradiation has been used in clinical practice as an alternative to injection of agents for SGB^{3,4}. In our previous study, we reported the usefulness of SGB-based treatment using xenon light (xenon phototherapy of the stellate ganglion, XPSG) for patients with tinnitus⁵.

In the present study, we further evaluated the therapeutic effects of XPSG on tinnitus using the tinnitus handicap inventory (THI) and a

numerical rating scale (NRS), in comparison with patients without XPSG.

Materials and Methods

1) Subjects

XPSG group and non-XPSG group were defined as patients treated with XPSG for 3 months and those with sham treatment followed by XPSG for 3 months, respectively. Subjects of XPSG group included 43 patients, consisting of 26 males and 17 females, with chronic tinnitus who visited the Department of Otorhinolaryngology of Fukushima Medical University Hospital or the Hoshi General Hospital between April 2014 and November 2016. Subjects of non-XPSG group included 18 patients, consisting of 10 males and 8 females, with chronic tinnitus between January and November 2016. Patients with pulsatile or objective tinnitus were excluded. Patients with physical conditions such as auditory nerve tumor and inner ear malformations were also excluded.

2) Methods

This study was approved by the Ethics Committee of Fukushima Medical University (approval No. 1961). Patients were fully informed of the

clinical efficacy and side effects of XPSG before consenting to participate in the study. Conventional medicine for tinnitus such as vitamin supplements, drugs to improve blood circulation, and Chinese herbal remedies were avoided during the study period. The dose of anxiolytics or sleeping aids for anxiety or sleep disorders was gradually reduced toward no prescription while duly consulting with the patient.

The xenon phototherapy device PHOS-01 (NIHON IKO Co., Tokyo, Japan) was used to perform XPSG by emitting xenon light once every 4 seconds for 10 minutes toward the area around the stellate ganglion bilaterally in a supine position in a bright room (Fig. 1). In principle, XPSG was performed once a week for 3 months with an amount of 18 J/cm² energy per illumination session, resulting in 3,510 J/cm² in total 24 illumination sessions per phototherapy course. Similar procedure with emission of non-xenon light and beep but not irradiation was applied for the non-XPSG group. Patients in non-XPSG group were further treated with XPSG for 3 months after sham treatment periods.

3) Assessment

The effect of XPSG on tinnitus was subjectively evaluated at 3 months

after therapy initiation using THI and NRS. The severity of tinnitus was rated as a scale between 0 and 100, and was classified into 4 grades based on THI scores: no handicap (0–16), mild (18–36), moderate (38–56), and severe (58–100). The degree of agony was rated from 0 to 10 on a 11-point NRS. Higher score means severer symptoms.

4) Statistical analysis

Data were shown in mean \pm standard errors. Differences in scores between paired and unpaired two groups were compared using the Wilcoxon signed rank test and Mann-Whitney U test, respectively. All analyses were carried out using SPSS 24.0 software (SPSS Inc., Chicago, IL). In all tests, $p < 0.05$ was considered significant.

Results

1) Patients characteristics

Mean age of subjects of XPSG group and non-XPSG group were 64 ± 2.2 and 63 ± 3.0 years old, respectively. Mean disease duration in subjects of XPSG group and non-XPSG group were 38 ± 6.9 and 63 ± 11.0 months respectively. No significant differences were observed between two groups

with respect to both age and disease duration.

2) THI

In XPSG group, mean scores of THI before and after XPSG for 3 months were 54.1 ± 4.3 and 34.6 ± 3.5 , respectively, and this difference was significant ($p < 0.01$) (Table 1). According to severity grade, significant improvement after XPSG for 3 months were observed in patients with moderate ($p < 0.05$) and severe ($p < 0.01$) THI scores (Table 1, Fig. 2a). On the other hand, mean scores of THI before and after sham treatment in non-XPSG group were 54.4 ± 6.2 and 51.6 ± 6.7 , respectively, showing no significant improvement (Table 2). Mean score of THI after XPSG following sham treatment in non-XPSG group was 43.4 ± 6.1 , showing an almost significant trend forward improvement ($p = 0.06$) (Table 2). Comparison of THI score improvement between during XPSG in XPSG group and during sham treatment in non-XPSG group demonstrated significant difference ($p < 0.01$), confirming a therapeutic effect of XPSG.

2) NRS

In XPSG group, mean scores of NRS before and after XPSG for 3 months were 5.8 ± 0.4 and 4.4 ± 0.3 , respectively, and this difference was

significant ($p<0.01$) (Table 1). According to severity grade, significant improvement of NRS scores after XPSG for 3 months were observed in patients with moderate ($p<0.05$) and severe ($p<0.01$) THI scores (Table 1, Fig. 2b). On the other hand, mean scores of NRS before and after sham treatment in non-XPSG group were 5.8 ± 0.6 and 6.1 ± 0.6 , respectively, showing no significant improvement (Table 2). Mean score of NRS after XPSG following sham treatment in non-XPSG group was 5.3 ± 0.5 , showing an almost significant trend forward improvement ($p=0.07$) (Table 2). Comparison of NRS score improvement between during XPSG in XPSG group and during sham treatment in non-XPSG group demonstrated significant difference ($p<0.01$), confirming a therapeutic effect of XPSG.

Discussion

The phototherapy was reported as a treatment of the intractable skin ulcer for the first time in 1973⁶. There have been many reports with respect to phototherapy since then⁴. Xenon light is generated using xenon gas as a medium and is multi-wavelength light with broadband wavelength ranging from ultraviolet to infrared light⁷. The xenon light we used this time reached

approximately 7cm in depth, and the irradiation energy per one emission of light was 18 J/cm². There are one hundred and ninety-five times of emitted light by irradiation for ten minutes, and the total irradiation energy became 3,510 J/cm². The irradiated area by the probe is about 27 cm², which allowed xenon light to illuminate a wide area. Xenon light peaks around 700 to 900 nm, and thus has excellent water and blood permeability penetrating not only the surface layer, but also deep layers of biological materials. Due to its high energy, xenon light promotes vasodilation via the sympathetic nervous system and facilitates tissue restoration⁷.

The stellate ganglion is located anterior to the transverse process of the seventh cervical vertebra and posterior to the vertebral artery, and is approximately 2 cm in depth from the anterior surface of the neck⁸. Xenon light irradiation is expected to increase blood flow through functional suppression of stellate ganglion, suggesting that this technique is simple and safer than conventional SGB. However, local low temperature burns and malaise may occur as adverse effects. Actually, although the spectral range of xenon light is 260–1100 nm, the current device provides the light peaks around 700–900 nm where it is readily absorbed into the skin. However, in

the present study, we did not observe any XPSG-related adverse events, except for mild vertigo with spontaneous regression in one patient, suggesting that XPSG is thought to be a safe treatment approach even for elderly individuals. With regard to the effect on tinnitus, overall THI and NRS scores improved significantly after 3 months of XPSG, especially in patients with severe tinnitus.

Psychological factors such as mental vulnerability, anxiety, and stress aggravate tinnitus⁹. Accordingly, it is debatable whether xenon light improved tinnitus by increasing blood flow via vasodilation. In the non-XPSG group, which is served as control in the present study, we used a special probe that allows emission but inhibits illumination by the light. This was to reveal possible placebo effects, specifically the involvement of mental control mechanisms on the improvement of tinnitus because patients were being treated or had hope for satisfactory therapy outcomes. We found no significant difference in THI or NRS scores between the XPSG and non-XPSG groups. XPSG was subsequently performed under the same conditions, significantly improving THI scores after 3 months of XPSG.

The clinical efficacy of other treatment modalities for tinnitus was

reported to be 50% with cognitive behavioral therapy¹⁰, and 60 to 80% with tinnitus retraining therapy¹¹. In the present study, 22 (51%) of 43 cases demonstrated improvement of THI score by 20 or greater points, which was shown to be 95% confidence intervals¹², suggesting that XPSG is comparable with those methods.

The above findings showed that XPSG provided high levels of satisfaction to patients by significantly improving THI and NRS scores. However, our investigation of XPSG is still in the early phase. Identification of predictive factor for responder to this treatment may be also useful. In 22 responders showing improvement of THI scores 20 or greater points, a notable but not significant shift toward lower pitch was observed using pitch match (data not shown). In remaining 21 non-responder, no obvious change of pitch was observed (data not shown). Therefore, pitch match may be a possible way to identify a responder. Apart from neuro-otological assessment, conventional factors including thickness of the neck and body weight may be a candidate. However, those are not included in the present study. Further studies are required to establish this procedure as a potent treatment for severe tinnitus.

Conclusion

In conclusion, we demonstrated statistically significant improvement of both THI and NRS scores after XPSG for 3 months in patients with subjective tinnitus. Severe cases with high THI or NRS score showed greater improvement. On the other hand, no significant difference was observed between before and after sham treatment in non-XPSG group. XPSG is a possible treatment modality for patients with tinnitus.

Disclosure Statement

The author reported no conflicts of interest.

Acknowledgment

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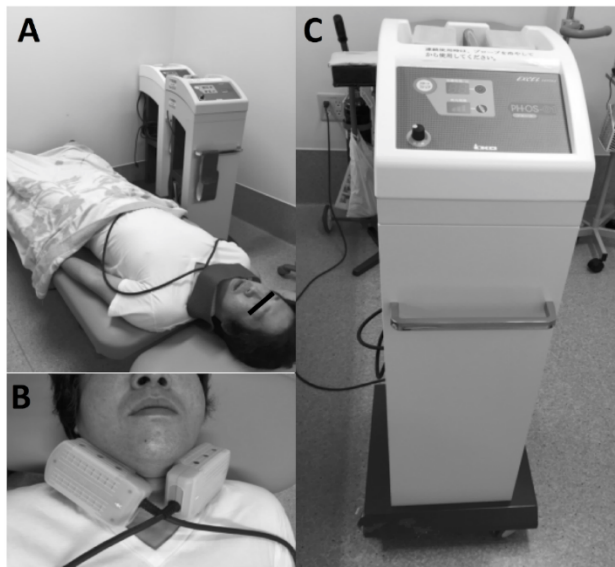


Figure 1.

Treatment was performed in a supine position (A). XPSG probes were placed around stellate ganglion regions (B). Appearance of xenon phototherapy device (C).

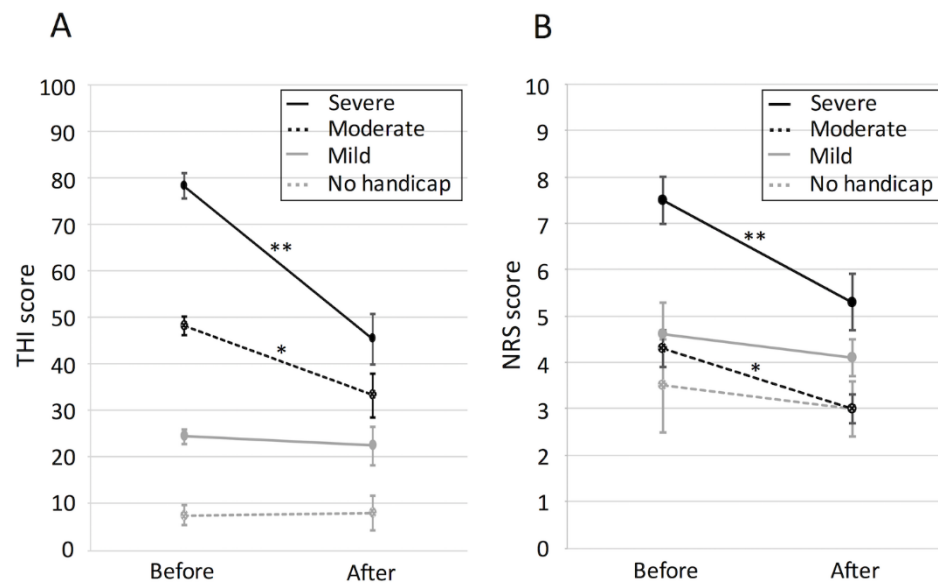


Figure 2.

THI (A) and NRS (B) scores before and 3 months after XPSG treatment in XPSG patient group according to severity grades.

*, $p < 0.05$; **, $p < 0.01$

Table 1 THI and NRS before and after XPSG in XPSG group

Severity of tinnitus (THI before treatment)	Number of Patients	THI score		NRS score	
		Before	3months	Before	3 months
No handicap	4	7.5 ± 2.2	8.0 ± 3.6	3.5 ± 1.0	3.0 ± 0.6
Mild	9	24.4 ± 1.6	22.4 ± 4.2	4.6 ± 0.7	4.1 ± 0.4
Moderate	9	48.2 ± 1.9	33.3 ± 4.7 *	4.3 ± 0.4	3.0 ± 0.3 *
Severe	21	78.3 ± 2.7	45.4 ± 5.5 **	7.5 ± 0.5	5.3 ± 0.6 **
Total	43	54.1 ± 4.3	34.6 ± 3.5 **	5.8 ± 0.4	4.4 ± 0.3 **

*, p<0.05; **, p<0.01

Table 2 THI and NRS in non-XPSG group

Number of Patients	THI score			NRS score		
	Before sham treatment	After sham treatment	3months after XPSG following sham	Before sham treatment	After sham treatment	3months after XPSG following sham
18	54.4 ± 6.2	51.6 ± 6.7	43.4 ± 6.1	5.8 ± 0.6	6.1 ± 0.6	5.3 ± 0.5